

Correlation between attention deficit hyperactivity disorder and bipolar disorder in children and adolescents: Systematic review

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Summary

Determining the correlation between affective bipolar disorder (BD) and attention deficit hyperactivity disorder (ADHD) in children and adolescents by choosing the most appropriate hypothesis explaining the nature of connection between these two diagnoses based on systematic review of literature.

An overview of literature published in MEDLINE/PubMed database and Google Scholar search engine between January 2008 and February 2019 concerning the correlation between BD and ADHD was performed. We selected articles in Polish or English published in journals, which were closely related to the topic and could be assigned to at least one of the four hypotheses.

Ultimately, 10 research papers were included in the review. The range of the papers' score was 3.5–9 according to adapted NOQAS scale, with mean score of 6.6 out of possible 9, which lead to a general average quality of the papers. In all the works the psychopathology of patients was evaluated according to DSM-IV diagnostic criteria.

The relationship between ADHD and BD in the children and adolescent population is not clear and an unambiguous hypothesis defining this correlation is not possible at this point. Further prospective research that provides evidence facilitating correct diagnosis as early as possible is essential as it has considerable influence on patients' course of disease and quality of life.

Key words: attention deficit hyperactivity disorder, bipolar disorders, attention deficit disorder with hyperactivity

Introduction

In the last decades, an increased interest in affective bipolar disorder (BD) in the population of children and adolescents has been observed in scientific literature. Given the suggested diagnostic differences between the children's form of the illness and the one observed in adults, a separate subtype dedicated to this age group is proposed (pediatric BD – PBD) [1]. This differentiation is crucial when taking into account the high diagnostic difficulty of PBD as well as persistent conviction that incidence of BD is scarce in the population of children and adolescents. In the meantime, the prevalence of BD in European population of children and adolescents has increased from 0.0025% in the years 1994–1995 to about 1% in 2002–2003 [2]. It is believed that up to 60% of BD patients had the first episode of the illness before the age of 20, and 22% of patients had the first symptoms before 12 [2, 3]. However, in current clinical practice, for most of the patients, the time from occurrence of the symptoms to final diagnosis and incorporation of proper treatment is still up to 10 years. In the meantime, 80% of those patients are treated for disorders concurrent with mood disorders, such as: adaptive disorders, anorexia nervosa or behavioral disorders [2, 4, 5].

The differences between clinical presentation of BD in children and adults are emphasized in the literature. In DSM-5, PBD has the same diagnostic criteria as adult BD (the only differences being: allowing “irritable mood” instead of “depressed mood” and “no result in achieving desired body mass” instead of its reduction) [2]. At the same time, the literature shows multiple sources indicating significant differences between these age groups. For example, Cichoń et al. [2] report that patients with PBD more often than those with BD experience depressive symptoms, aggression and serious emotional lability, and less often experience thought disorders (i.a., train of thought acceleration and logorrhea). Increase in psychomotor drive (occurring in 79% of children) and irritability (77%) are considered the cardinal symptoms of mania in children and adolescents [2]. Concurrently, increased sexual activity, which is considered one of the most distinctive symptoms of mania in adults [6], is only observed in 38% of PBD patients [7]. The differences in the course of PBD and BD can also be seen during the episodes. Mania and mixed episodes can last 3–4 years in children, and, taking into account the differences in their course, can prevent differentiating between distinct episodes of the illness and consequently accurate diagnosis [7, 8].

The suggested clinical picture of PBD may imply association with attention deficit hyperactivity disorder (ADHD). Currently in the literature the frequency of ADHD is described as 3–10% among children and adolescents and 4–5% among adults [9]. According to DSM-5 definition, ADHD is a disorder that is defined by attention deficit with impulsiveness and hyperactivity that last at least half a year and do not correlate with proper developmental age. In the case of uncharacteristic clinical picture

there is a diagnostic category of another specified disorder with attention deficit and hyperactivity in which, without meeting the criteria for ADHD diagnosis, a person experiences severe limitation in social conduct. Frequent comorbidity of ADHD and BD is stressed in the literature, especially in the population of children and adolescents [2] where this frequency is estimated at 53% [7]. According to Donfrancesco et al. [10], irritability and inconclusive episodes observed in PBD may be linked with co-occurrence of ADHD. This could indicate ADHD as having an influence on specific traits of BD in the population of children and adolescents, such as: (1) earlier onset of illness, (2) severity of illness, (3) higher insensitivity to therapy (lower efficiency of lithium) [10].

Significant comorbidity and high degree of overlapping of ADHD and mania/mixed episode of PBD symptoms can constitute a serious diagnostic difficulty in differentiating between these two conditions. For example, behavioral disorders comorbid with ADHD may clinically resemble mania or mixed episodes [2]. According to Martin et al., clinically, ADHD and PBD do not show statistically significant differences in frequency of irritability, increased attention shifting, loquaciousness or logorrhea, or increased psychomotor drive [11]. However, due to pathophysiological differences between these two conditions, those symptoms differ slightly in clinical manifestation. Additionally, there are distinctive symptoms specific to ADHD and PBD. These differences can be observed in, for example, hyperactivity scope, which in PBD patients manifests as intermittent episodes of increased hyperactivity or considerable agitation, often co-occurring with increased impulsiveness and heightened aggressive behaviors [12]. Whereas a persistent, unchanging with time agitation and restlessness that intensifies during activities involving particular concentration and long-lasting effort can be observed in ADHD patients [12].

Another example is increased aggression in both groups. All types of aggression (verbal aggression, anger, decreased control, impulsive behaviors leading to damage of goods or excessive physical aggression) are relatively common in BD stemming from periodic increased irritability [12, 13]. While in ADHD aggressive behaviors are constant, derive from substantial impulsiveness and are associated with frustration [12]. Both disorders cause learning difficulties, however, in PBD patients those difficulties are related to current illness phase, while in ADHD patients they are consistent and result from difficulties in concentration and maintaining attention [2]. Another aspect would be sleep disorders, which in ADHD take the form of difficulties with initiating night sleep but without simultaneous decreased need for sleep, which is typical for PBD, and manifests as a decreased sleep time with subjectively maintained sleep quality [2].

Differentiating mania or mixed episodes of PBD and ADHD lies in distinctive symptoms for each of these conditions. For PBD these symptoms include: increased mood (euphoria), increased self-esteem, increased sexual energy, hallucinations, and

aforementioned decreased need for sleep [7]. However, this type of “marker” symptoms change with patients’ age, also some depressive symptoms (e.g., substantial sadness, appetite change or suicidal thoughts) are a vital diagnostic element only after the age of 7 [12, 14, 15]. Meanwhile, in a retrospective study conducted by Fergus et al. [14], increased mood, decreased night sleep, irritability and, in some cases, increased sexual behaviors occurred before the age of 6 in children that would develop PBD. Using KSADS questionnaire in out-patients it was observed that short and elongated periods of increased mood have been found much more frequently in BD patients than in ADHD patients as early as 3 years old [12, 15]. Table 1 shows a compilation of BD and ADHD symptoms [2].

Table 1. **Manic symptoms which can be found in ADHD children and adolescents**

Diagnostic criteria of mania	(+) – symptoms that occur in ADHD children and adolescents (-) – symptoms that do not occur in ADHD children and adolescents
1. Increased activity and physical restlessness	+
2. Increased talking (need for speaking)	+
3. Racing thoughts or subjective feeling of their acceleration	-
4. Loss of normal social inhibitions leading to maladjusted behaviors	+
5. Decreased need for sleep	-
6. Increased self-esteem or sense of superiority	-
7. Reversibility or constant changes of activities or plans	+
8. Blunt or reckless behaviors that underestimate risks	+
9. Increased sexual energy or sexual indiscretions	-

Materials

The following paper is a review of literature concerning correlation between PBD and ADHD published between January 2008 and February 2019. MEDLINE/PubMed and Google Scholar databases were used for research. The following terms were used: ADHD, Attention Deficit Disorders with Hyperactivity, Attention Deficit Hyperactivity Disorders, Attention Deficit-Hyperactivity Disorder, Attention Deficit-Hyperactivity Disorders, Deficit-Hyperactivity Disorder, Attention, Bipolar Affective Disorder, Bipolar Disorders, Disorder, Bipolar, Psychosis, Manic-Depressive, Psychosis, Manic Depressive, Manic-Depressive Psychosis.

Method

The first step of selecting the literature was assessment of compliance of papers with the topic based on analysis of titles. Second step was analysis of abstracts based on considered features, study and control group characteristics and methodology. In the third step, a preliminary analysis of full texts was performed based on previously established criteria which were as follows:

1. Articles published between January 2008 and February 2019;
2. Articles published in Polish or English;
3. Articles published in journals (book chapters were not taken into consideration);
4. Articles closely related to the topic of this review and possible to be assign to one of the few hypotheses (reviews were not taken into consideration);
5. Articles in which methods of the study were clearly and understandably presented (providing inclusion and exclusion criteria, patients' demographic data, data about the diagnostic process of bipolar disorder and attention deficit hyperactivity disorder);
6. Articles where the study was conducted on the population of children and adolescents;
7. Articles which, according to NOQAS, had a score higher than 3.5 points.

Articles qualified for review were analyzed in terms of number of patients in groups, manner of diagnosis verification, age of patients at the time of the study, quantitative and qualitative parameters of results, limitations, and conclusions made by authors. Subsequently, every paper was assigned to one or more hypotheses presupposed in the literature regarding the relationship between BD and ADHD. Four main hypotheses occurring in the literature that describe the nature of the relationship between these two conditions are presented below:

1. ADHD in children and adolescents is a prodrome of affective bipolar disorder;
2. ADHD and BD are strongly correlated and have a high rate of co-occurrence in the population of children and adolescents;
3. Comorbidity of ADHD and BD in children and adolescents is a distinct phenotype that is, in fact, a subtype of one of these disorders.
4. Due to major diagnostic difficulty, ADHD and BD are often misdiagnosed in the population of children and adolescents.

Articles were qualitatively evaluated by authors using modified NOQAS (Newcastle-Ottawa Quality Assessment Scale for Case Control Studies) (points were used instead of stars). The results of this evaluation were put into a table. Aforementioned scale assesses publications in three categories: (1) method of study and control group selection, (2) homogeneity of both of the groups and (3) process of verifying the diagnosis/exposure to examined variable in a study group. Each paper

could gain 9 points at most. In subsections 1, 3, 6 and 8, a paper could gain 1, 0.5 or 0 points. In subsections 2, 4, 7, a paper could gain 1 or 0 points. In subsection 5, assessing comparability of control and study groups, a paper could gain 2, 1 or 0 points. Ultimately, 21 articles were included into the analysis. Detailed selection procedure was shown in Figure 1.

Results

Table 2. Review of the articles

Publication	Group description	Type of study	Publication characteristic (results, conclusions and additional information)
Luckenbaugh et al. 2009 [15]	<p>Study group 1 (clinical population) ADHD without BD n = 22</p> <p>Study group 2 (clinical population): BD n = 27</p> <p>Comorbid ADHD: n = 18 (67%)</p> <p>Age of BD onset <9 (n = 14)</p> <p>Comorbid ADHD: n = 11 (71%)</p> <p>Age of BD onset >9 (n = 8)</p> <p>Comorbid ADHD: n = 4 (50%)</p> <p>Control group (general population, some patients were siblings of control group): n = 26</p>	retrospective	<p>BD patients (mean age 7.2 (SD: 4.1) years). 67% (n = 18) of patients were also diagnosed with ADHD.</p> <p>In the case of patients <9 years old, 71% (n = 11) were also diagnosed with ADHD</p> <p>In the case of patients >9 years old, 50% (n = 4) were also diagnosed with ADHD.</p> <p>These differences were assessed by the authors as statistically significant.</p> <p>High mood and sleep disorders as differentiating factors of ADHD and BD as early as 3 years old.</p> <p>There is a statistically significant difference between the clinical picture of BD with onset before and after 9 years old. For children with BD the onset of symptoms is rapid and acute and the symptoms themselves are more severe compared to ADHD.</p> <p>Other features that could differentiate BD and ADHD are:</p> <p>BD in first-degree relatives;</p> <p>Lack of improvement or worsening of symptoms in response to psychostimulant medication;</p> <p>Prior BD diagnosis is associated with milder course and better prognosis.</p>

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<p>Biederman et al. 2009 [16]</p>	<p>All: MDD n = 168 (118 subjects, 50 siblings)</p> <p>Study group 1 (clinical population): MDD with ADHD n = 115 (95 subjects, 20 siblings)</p> <p>PBDI developed during the study: 29 (27.6%) [17.1% PBDI, 10.5% subliminal PBDI] out of 105;</p> <p>Control group (patients' siblings): MDD n = 53 (23 subjects, 30 siblings) PBDI developed during the study: 3 (6%) [4.0% PBDI, 2.0% subliminal PBDI] out of 50</p>	<p>prospective</p>	<p>168 patients aged 6–18 diagnosed with major depressive disorder (MDD), out of which 115 with comorbid ADHD were observed over the period of 7 years.</p> <p>27.6% (n = 29) of patients with comorbid ADHD were diagnosed with BD over the course of the study.</p> <p>6% (n = 9) of patients without ADHD were diagnosed with BD over the course of the study.</p> <p>ADHD is a risk factor of BD for patients with unipolar disorder because a much higher percentage of the study group developed BD compared to controls, which was assessed as statistically significant (27.6% in the study group compared to 6% in the control group). In the study group a risk factor for full BD was initial subliminal BD (70% compared to 17%, $z = 3.17$, $p = 0.002$).</p> <p>For all patients in the control group with the diagnosis of unipolar disorder and subliminal BD at the beginning of the study was confirmed at the end of the study. Frequency of symptoms occurrence among 6 patients from the study group with ADHD and subliminal BD diagnosis at the beginning of the study that had BD diagnosed at the end of the study was as follows: distraction (100%), racing thoughts (83%), decreased need for sleep (67%), irritability (50%), increased energy and weak judgement (33%), increased mood, narcissistic behavior and accelerated speech (17%). Behavioral disorder, mood disorder in patients' parents and problems with behavior at school were determined as risk factors for BD.</p> <p>Only 5% of the patients (1/20) with no BD risk factors, 24% (11/46) with one risk factor ($p = 0.047$ compared to the previous group) and 32% (9/28) with two risk factors ($p = 0.03$ compared to the previous group) were diagnosed with BD at the end of the assessment. Significantly increased risk was present in patients with all three risk factors, 73% (8/11) of these patients were diagnosed with BD. Thus, physicians should carefully monitor patients with unipolar disorders, ADHD and many risk factors of BD development.</p>
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<p>Uchida et al. 2015 [17]</p>	<p>All: n = 404</p> <p>Study group (clinical population): ADHD n = 208</p> <p>Comorbid PBDI: 31 (11%) at the beginning of the study, additionally, in 12% BD was diagnosed after 4-year observation</p> <p>Control group (patients recruited from psychiatric and pediatric databases along with their first-degree relatives): n = 196 Comorbid BD: 0 (0%)</p>	<p>prospective</p>	<p>522 patients aged 6–17 (at the onset of the study) observed over 11 years. 280 patients diagnosed with ADHD.</p> <p>23% of ADHD patients were diagnosed with BD at the end of observation (11% were already diagnosed at the beginning of the study).</p> <p>In the control group, no one met the criteria for BD diagnosis during the whole period of observation.</p> <p>High rate of comorbidity of BD and ADHD did not occur due to overlapping symptoms of both disorders. After excluding overlapping symptoms (talkativeness, distraction and psychomotor hyperactivity) most patients could still be assessed with diagnostic symptoms of BD and ADHD. This meant that comorbidity of these two disorders is not only due to error in methodology resulting from overlapping diagnostic criteria.</p> <p>In the population of children with ADHD and BD, a more commonly positive family history of BD in first-degree relatives was noticed compared to ADHD children without BD. BD starting in childhood may be a subtype of BD or ADHD considering aforementioned analysis of familial occurrence proved that clinical picture of comorbid BD and ADHD differs from isolated ADHD.</p>
<p>Biederman et al. 2014 [18]</p>	<p>Study group (clinical population): ADHD and MDD n = 103</p> <p>BD developed in the 11.4-year observation: n = 24 (23%) [n = 4 (16.7%) subliminal PBDI at the beginning of the study, n = 20 (83.3%) no subliminal PBDI at the beginning of the study].</p> <p>No BD development during 11.4-year observation period: 79 (77%)</p>	<p>prospective</p>	<p>103 patients (mean age 10.7; (SD 2.9)) diagnosed with MDD and ADHD, with 7 of them presenting subliminal BD, were observed over 11.4 years.</p> <p>In the subliminal BD group, 57% of patients developed type 1 BD.</p> <p>In the group without subliminal BD, 21% developed type 1 BD.</p> <p>Subliminal affective bipolar disorder comorbid with ADHD occurring in children is a risk factor of developing BD and MDD during the later years of adolescence and early years of maturity seeing how the results of this study were deemed statistically significant.</p> <p>This implies a necessity for a careful treatment selection in children with subliminal affective bipolar disorder comorbid with MDD with special regard to the possibility of occurrence of mania while using antidepressant drugs.</p> <p>Patients from the study group that were diagnosed with BD did not differ from the study group patients without BD in terms of: sex, age at the start of the study, age at the end of the study, and socio-economic status.</p>

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Tandon et al. 2016 [19]	<p>All: n = 251</p> <p>Study group (clinical population): n = 159</p> <p>ADHD n = 75</p> <p>BD n = 84</p> <p>comorbid ADHD at the beginning of the study: n = 81 (87%) out of n = 93</p> <p>Control group (recruitment by randomized questionnaire, which allowed to select the participants fitting PBDI group based on socio-demographic criteria): n = 92</p>	prospective	<p>286 patients (at the beginning of the study) aged 7–16 were observed biannually for 10 or 12 years. Out of them, 81 patients were diagnosed with ADHD and 93 with BD (at baseline 87.1% that had type 1 BD diagnosis were additionally diagnosed with ADHD). Participants were divided into 4 classes in accordance with the severity of ADHD.</p> <p>In class IV, comorbidity of ODD and MDD was higher than in class III, which was assessed as statistically significant.</p> <p>Class IV patients were younger than other groups, which was statistically significant. However, patients in class III were younger than class II patients, which was also statistically significant. Classes III and IV had more boys than girls compared to classes I and II, which was statistically significant.</p> <p>In class IV, there were 53.6% (n = 30) of patients with ADHD and 46.4% (n = 26) with mania. After 10-year observation the number of ADHD patients increased to 100% (n = 56) and 75% (n = 42) of patients presented mania symptoms.</p> <p>In class 1, there were no patients with ADHD. 4.2% (n = 4) were diagnosed with BD. After 10-year observation 13.5% (n = 13) had ADHD and 5.2% (n = 5) presented mania symptoms.</p> <p>Participants from class I received less stimulating medication compared to other classes, which was statistically significant. Moreover, patients from class II received less stimulating medication than patients from class IV, which was statistically significant.</p>
Doerfler et al. 2011 [20]	<p>Whole study group (clinical population): n = 310</p> <p>Study group 1: ADHD n = 249</p> <p>Comorbid BD: n = 18 (7.4%)</p> <p>Study group 2: BD: n = 27</p> <p>Comorbid ADHD: n = 20 (74%)</p>	prospective	<p>27 patients diagnosed with BD; 249 patients diagnosed with ADHD (mean age: 10.2 (SD: 3.3) years).</p> <p>20% of patients with earlier BD diagnosis were additionally diagnosed with ADHD.</p> <p>Overlapping of the ADHD and BD diagnoses was asymmetric considering only 7.4% of patients with previous ADHD diagnosis being diagnosed with comorbid BD.</p> <p>BD patients were older than only ADHD patients. BD patients showed increased verbal and reactive aggression and depressive symptoms compared to patients with only ADHD diagnosis, which was a statistically significant difference. In children with BD, the symptoms were also more severe than in ADHD children, which was a statistically significant difference.</p>

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<p>Donfrancesco et al. 2011 [10]</p>	<p>All: n = 273</p> <p>Study group (clinical population): ADHD n = 173</p> <p>ADHD without BD: 144 (83%)</p> <p>Comorbid BD: 29 (17%) [16 (55.2%) BD-NOS, 10 (34.5%) BD II, 3 (10.3% BD I]</p> <p>Control group (participants recruited by questionnaire from the same area of Rome, same sex, age and race as study group): n = 100</p> <p>Comorbid BD: 1 (1%)</p>	<p>prospective</p>	<p>173 patients with ADHD aged 6–17.5 and 100 participants aged 6–17 without any diagnosis.</p> <p>17% of ADHD patients were diagnosed with BD, compared to only 1% of participants without the diagnosis, which was statistically significant.</p> <p>72% (n = 21) of ADHD patients that were diagnosed with BD presented mixed type of ADHD. In addition, the percentage of patients with mixed type of ADHD was significantly higher among the patients with both ADHD and BD comparing to the group with ADHD only.</p> <p>38% (n = 11) of ADHD patients with comorbid BD presented severe hyperactivity during the first 2 years of their life, 10% (n = 3) presented euphoria during the first 2–3 years of their life. Additionally, depressive episodes in years 6–8 occurred in 24% (n = 7) of patients, which was statistically significant. These results point to depression with early onset as a risk factor of comorbid BD.</p> <p>55% of patients with BD and ADHD diagnosis presented BD-NOS, which indicates an atypical clinical manifestation of BD in patients with BD and previous ADHD which is characterized by chronic course of illness and irritability as characteristic elements.</p> <p>High ADHD-RS score (ADHD assessment scale), specifically subscore of hyperactivity-impulsiveness may be a risk factor for BD development due to patients with BD and ADHD having higher score on hyperactivity-impulsiveness subscale and higher total ADHD-RS score compared to patients with isolated ADHD, which was statistically significant.</p> <p>Affective disorders are characterized by higher familial correlation than ADHD because among children with positive family history for psychiatric disorders one third covered BD and depression and only 18.5% ADHD.</p> <p>Due to the lack of group with isolated BD, it cannot be proven that some ADHD symptoms with comorbid BD are specific to this comorbidity rather than being only present in BD (e.g., high rate of comorbid psychiatric disorders).</p>
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<p>Arnold et al. 2011 [21]</p>	<p>Study group 1 (clinical population): ADHD n = 421</p> <p>Study group 2 (clinical population): BD: n = 45</p> <p>Study group 3 (clinical population): BD + ADHD n = 117</p> <p>Control group (clinical population): n = 124</p>	<p>prospective</p>	<p>707 participants, out of which 421 with ADHD, 45 with BD, 117 with both ADHD and BD, everyone aged 6–12.</p> <p>In this study, comorbidity of ADHD and BD was found in 16.5% of patients.</p> <p>ADHD and BD group did not differ in terms of onset of mood disorders from only BD group.</p> <p>High percentage of comorbidity of ADHD and BD could result to a larger extent from frequent occurrence of both disorders and their many symptoms that are common in the population of children and adolescents, than from ADHD alone being the factor for BD development.</p> <p>Age of the first patient visit turned out to be statistically significant and lower for patients with double diagnosis than for patients from BD group (9.6 vs. 10.5 years). However, this does not support the first hypothesis stating that in patients with double diagnosis symptoms occur earlier than in patients with isolated BD.</p> <p>Children with ADHD and comorbid BD had more severe attention deficit, hyperactivity and impulsiveness than those with isolated ADHD, which was statistically significant. It was proven that children with double diagnosis presented with more severe mania symptoms than children with only ADHD, which was statistically significant, but not than children with only BD.</p> <p>Overall functioning of the patients was more impaired in children with double diagnosis, which was statistically significant.</p> <p>It is worth mentioning that attention deficit was most common in the case of two comorbid disorders (94%), then in children with ADHD (86%) and least common in BD (51%).</p> <p>ADHD is more chronic than mood disorders which tend to have episodic varied incidents. ADHD symptoms worsen in comorbid disorders, however, this tendency does not apply to all mania symptoms.</p>
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<p>Serrano et al. 2013 [22]</p>	<p>All (clinical population): ADHD n = 100 Study group 1: BD-NOS n = 6 (6%) Study group 2: BD-DSM (diagnosed according to DSM-IV criteria) n = 8 Control group (clinical population): n = 86</p>	<p>prospective</p>	<p>100 ADHD patients aged 8–17, 14% presenting comorbid bipolar disorders.</p> <p>71% (n = 10%) of patient with comorbid bipolar disorders were found to have episodes of euphoria and expansive mood.</p> <p>100% (n = 14) of patients with comorbid bipolar disorders presented irritability, with 29% (n = 4) having irritability being the only symptom of mood disorder, without accompanying euphoria or mania (all of these cases were from BD-NOS group).</p> <p>Mean age of mania symptoms onset in group with comorbid bipolar disorder was 11 (SD: 4).</p> <p>Participants from the group with comorbid bipolar disorders were older than those without comorbid bipolar disorders, which was statistically significant.</p> <p>No statistically significant differences in severity of ADHD symptoms occurred between BD group and patients without BD according to CPRS-48 (Conners' Parent Rating Scale).</p> <p>Statistically significant higher occurrence of hyperactive-impulsive type symptoms was shown for patients with BD compared to control.</p> <p>Frequency of ADHD symptoms was similar in assessment of the parents of patients in both study and control groups, however, the rate of these symptoms was higher for parents of BD children than for parents of children without BD, which was statistically significant.</p>
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<p>McGough et al. 2008 [23]</p>	<p>270 families were included in the study and that was 540 children and 519 parents recruited by diagnosing ADHD according to DSM-IV in at least 1 of the children and the other having ADHD diagnosis or suspicion of ADHD diagnosis. 540 children were included into detailed assessment.</p> <p>Study group 1: BD-CBCL [BD diagnosed according to CBCL (Child Behavior Checklist) with high scores in all CBCL subscales] n = 45 Comorbid BD: n = 3 (6.6%)</p> <p>Study group 2: BD-AP CBCL [BD diagnosed as a high score in AP (Attention Problems) CBCL subscale only] n = 3 Comorbid BD: n = 2 (1.8%)</p> <p>Control group: n = 392 Comorbid BD: n = 5 (1.3%)</p>	<p>prospective</p>	<p>540 participants with ADHD aged 5-18 (mean age 10.6; (SD: 3.2) years) took part in this study.</p> <p>Only 2% of ADHD patients were found with comorbid bipolar disorders. This percentage, lower than in other studies, could be the result of error in choosing a well-functioning group of patients.</p> <p>In this study, it was pointed out that some genome regions within 2q chromosome require further research regarding possible genetic correlation between ADHD and BD.</p> <p>Among the ADHD patients, n = 10 (1.9%) were found diagnosed with BD: n = 5 (1.3%) patients from control, n = 3 (6.6%) patients in CBCL-BD and n = 2 (1.8%) in BD-AP CBCL.</p>
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Discussion

In the first step of analysis, based on titles, 615 articles were identified. During the analysis of references, another 22 articles were included. Subsequently, 132–144 articles, depending on author, were included into the second step – abstract analysis. 84–87 articles were included into the third step. During the third step articles that did not meet inclusion and exclusion criteria, were duplicates or were not available were

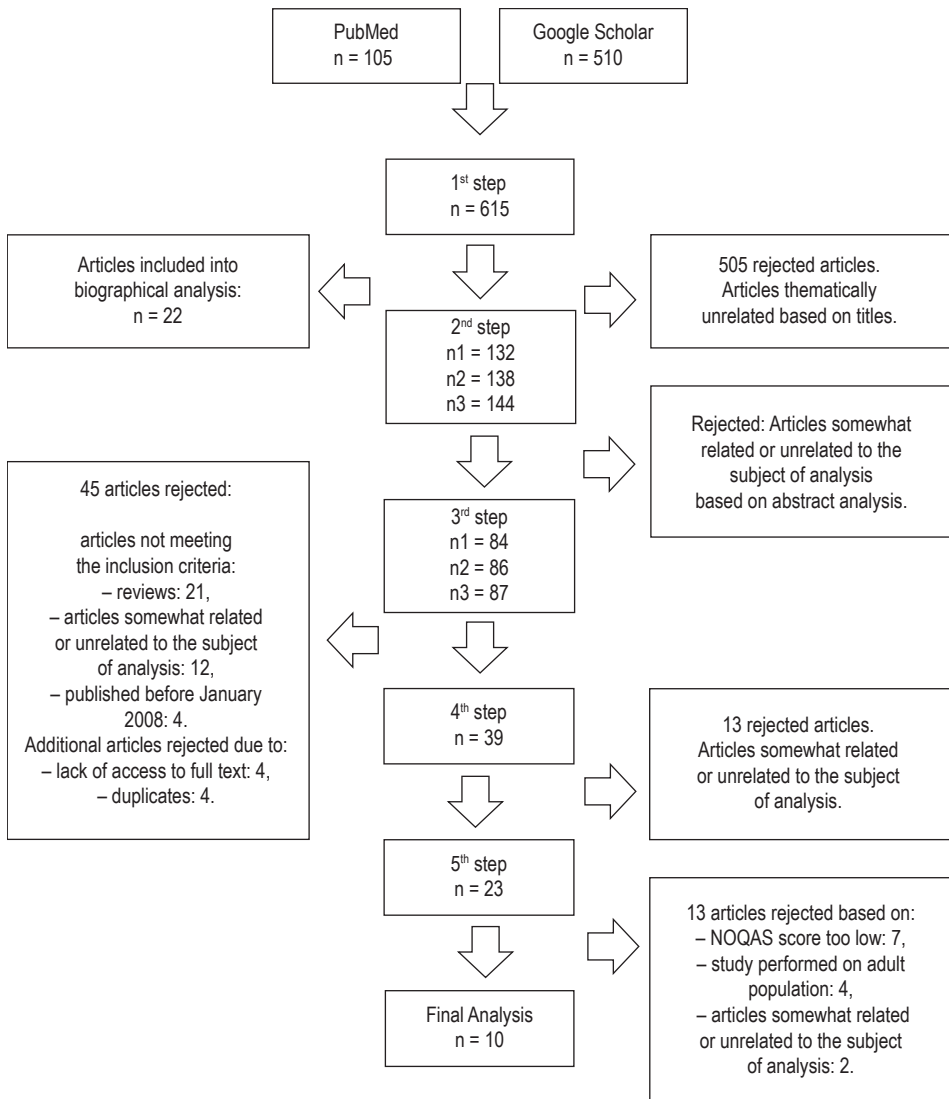


Figure 1. Article selection procedure

rejected, leaving 39 papers being included into the fourth step. After initial full-text analysis, 23 papers were qualified for the next step. At this point articles were rejected based on:

- (1) study performed on adult population – 4 papers;
- (2) Lack of sufficient compatibility with the subject of analysis – 2 papers;
- (3) NOQAS score of 3.5 or lower – 7 papers.

Ultimately, 10 publications were included into this review. The evaluated articles are presented in Table 2. A thorough review of publications is presented in Figure 1.

The range of scores in adapted NOQAS was 3.5–9 points., mean result was 6.6 with the maximum of 9 points., which culminated in relatively average quality of articles. 7 out of 10 articles used the K-SADS diagnostic interview (K-SADS, K-SADS-E, K-SADS-PL or WASH-U-KSADS). In all of the works patients' psychopathology was assessed according to DSM-IV.

Conclusion

The presented literature review demonstrated the conflict related to the correlation between affective bipolar disorder and ADHD in the population of children and adolescents. Many scientific reports indicate a significant comorbidity of these two medical conditions in both children and adolescent, and adult populations [24–27], as well as frequent family history of mood disorders in ADHD patients [26]. Tramontina et al. [28] indicated ADHD as being the disorder most frequently comorbid with BD in children and adolescents, which was confirmed by other authors [24, 27, 29, 30]. Thus, the relation between ADHD and BD seems indisputable, however, the question of its origin remains open. In literature, various concepts regarding this issue arise, starting from a hypothesis that undefined pathogenetic factors of ADHD increase the risk of BD, and going as far as suggesting that ADHD is, in fact, a distinctive subtype of BD characteristic for the population of children and adolescents. The reason for this uncertainty is similarity of clinical picture of these two disorders, especially during development stages when the predominant BD symptoms are irritability, increased psychomotor drive and lack of, unmistakable in adults, distinct episodicity of the disorder. This type of clinical picture may, for obvious reasons, suggest types of ADHD with comorbid irritability, which may account for compelling diagnostic challenge. Accurate differential diagnosis in these cases is essential considering that the duration of untreated, or worse, improperly diagnosed BD significantly worsens prognosis [31]. Therefore, understanding of this correlation is crucial, as well as determining the symptoms that may enable adequately early diagnosis and differentiation of these conditions.

Numerous reports indicating ADHD as a clinical risk factor of BD have been found in literature [31–34]. It implies the necessity for clinicians for attentive observation of

children and adolescents with ADHD diagnosis for possible BD development. In this context, a significant issue is the age of transition between ADHD to BD. For instance, in the study by Sachs et al. [36], ADHD and BD patients presented the first typical BD symptoms at the age of 12.

Another intriguing issue is conversion of ADHD to BD. Kutcher et al. [37] diagnosed ADHD on average a year before the development of bipolar disorder. On the other hand, Biederman et al. [38] diagnosed BD in 11% of ADHD children at the beginning of the study and later, after 4-year observation period, in another 12%. Wozniak et al. [39] indicate that ADHD can be considered as a prodrome of affective bipolar disorder. Out of 43 manic children, 98% also presented ADHD, whereas only 20% of patients out of 206 with ADHD were diagnosed with mania. Moreover, in this study, the duration of illness amounted to 68% of children's lifespan in ADHD group while only 38% in the group of children with mania. Surprisingly, 77% of children with mania also presented severe and constant irritability, 84% were described as having a chronic course of illness and 84% presented mixed episodes of the illness [39].

A different hypothesis regarding the nature of the relationship between the two disorders is suggesting that ADHD is actually a subtype of BD distinct for the population of children and adolescents. This concept stems from the similarity of clinical pictures of these two conditions in this population and from frequent positive family history of affective disorders in ADHD patients [27]. This type of approach was put forward in the study by Geller et al. [40], where it was suggested that ADHD may constitute a type of affective bipolar disorder occurring in a specific age group. Additionally, this hypothesis appears to be supported by results of genetic studies. Genetic variation amongst the most common dopamine receptor in the brain – DRD1 was linked to both ADHD and BD [41]. Furthermore, for both of these diseases, risky alleles of *TPH2* gene were identified. This points to a possible shared genetic background of BD and ADHD. However, it is critical to have in mind that, although the results of these studies are promising, they have significant limitations in the form of application of non-homogenous methodology and small study group [41].

Another issue worth discussing is the risk of underdiagnosis or overdiagnosis related to aforementioned difficulty in differentiation between ADHD and some types of BD. Geller et al. [40] have shown in their study that this difficulty is predominant in patients aged 12 or less. Moreover, the authors point out that until more scientific data on affective bipolar disorder in the population of children and adolescents is available, doctors will be having diagnostic difficulties in differentiating comorbid ADHD and BD from isolated ADHD. Wozniak et al. [39] share a similar thesis stressing that because of frequent comorbidity of early onset mania at the beginning of ADHD, along with the presence of a number of similar symptoms of both disorders (impulsiveness, emotional lability, distraction, and hyperactivity), further studies enabling determination of the relationship between these two conditions are essential. Faedda et al. [24]

describe a comparable clinical manifestation and a high percentage of incidence of other psychiatric disorders, including ADHD, as leading to underdiagnosis of BD in children. In this publication, at the beginning, 90% of patients were diagnosed with ADHD or other disorder and only 10% were diagnosed with affective bipolar disorder despite positive family histories for affective disorders or addictions and recurrent symptoms of affective disorder. On the other hand, Tramontina et al. [28] explain the misdiagnosis of BD as severe ADHD with a high percentage of co-occurrence of both of these disorders.

In summary, from the data obtained from the literature emerges a rather consistent conclusion regarding a relationship between ADHD and BD in children and adolescents. The differences in demographic profile of the groups, non-homogenous methodology and varied quality of the available studies (measured with NOQAS) make an unambiguous determination of the nature of this relationship based on feasible data impossible. Reliable, prospective studies that enable identification of correlation between ADHD and BD in the population of children and adolescents that would deliver evidence facilitating correct diagnosis as early as possible are necessary. While treating patients with ADHD it is vital to notice the course of the illness and potential occurrence of symptoms suggesting development of early onset BD [35]. Accurate diagnosis enables selection of adequate treatment, which has a considerable influence on the course of the illness, which, in turn, translates directly onto quality of life of the patients.

A limitation of our study was adopting January 2008 to February 2019 timeframe. The discussed disorders were conceptualized similarly to today's standards, which means that older articles could have been still relevant. Nevertheless, previous publications were analyzed in papers from 2003 [42] and 2008 [43]. In both papers the authors drew attention to necessity of further studies of relationship between ADHD and BD in the population of children and adolescents due to the small amount of data available in literature in the given times. Thus, the aim of our systematic review was to summarize more recent studies and to indicate the need for further research on this issue as well as the need to change the methodological approach to a more comprehensive one, including various hypotheses regarding the relationship between ADHD and bipolar disorder in the population of children and adolescents

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